7. Surface Erosions

> *"Erosion of proteoglycan-rich and smooth muscle cell-rich plaques lacking a superficial lipid core or plaque rupture is a frequent finding in sudden death due to coronary thrombosis."*
> *A Farb, etal., [110]*

The IA causing atherosclerosis is believed to enter the artery wall from the circulating blood through a breach in endothelial integrity, localizing in the intima and initiating the injurious, destructive process that leads to plaque development [18]. The IA, however, is not necessarily confined to the depths of the intima, but may also localize at the endothelial surface overlying the plaque and cause injury, erosion, and destruction of the endothelium and subendothelial tissue (Figure 7)[110]. The histologic features surrounding these surface erosions are similar if not identical to those found in the deeper necrotic core, including the presence of macrophage foam cells, tissue debris, and evidence of tissue digestion and destruction. Both deep and superficial lesions may be caused by the same IA.

Surface erosions occur only over atherosclerotic plaques, not over normal wall. They therefore follow and are superimposed on an already established plaque. This means there is a time interval between initial plaque formation and the subsequent development of surface erosions, suggesting that the IA initially traversed the endothelial barrier without affecting or injuring the endothelial cell. If both deep and superficial lesions are caused by the same IA, but at different time intervals, then the IA must be present and persist in the circulating blood for long periods of time. The subsequent development of a surface erosion results in two active, destructive processes proceeding simultaneously, but at separate locations within a plaque, with surface erosions arising separately, independent of the deeper injurious process.

Endothelial Vulnerability or Dysfunction

The observation that surface erosions are limited to the endothelial surface overlying a plaque suggests the endothelium in this region has become altered in some way [18,111] and may be more vulnerable, dysfunctional, or susceptible to the IA than is the endothelium over normal wall. Something or some agent contained or acting within an atherosclerotic plaque appears to adversely affect the overlying endothelium, particularly in its ability to withstand injury by the IA [111]. Endothelial dysfunction or injury is apparently multifactorial in origin [18], but this does not mean the IA is also multifactorial. However, surface erosions are not present over every plaque so there may be variable responses by the endothelium overlying atherosclerotic plaques.

Judging by the histologic changes taking place at the endothelial surface, an IA, such as a virus, may actually enter the endothelial cell and alter intracellular mechanisms and functions [112]. For example, Figure 17A shows a single layer of endothelial cells distended with lipid, suggesting they have transformed into macrophages, ingested lipid, and subsequently developed into macrophage foam cells. The plaque tissue underlying this layer of endothelial cells, although diseased and abnormal, does not contain macrophage foam cells. The IA may have targeted and entered these endothelial cells directly.

The macrophage foam cell is an afflicted cell that is unable to migrate within tissue, to regulate the uptake of lipid or to maintain endothelial integrity [30]. The protective, defensive responses that characterize a normally functioning macrophage have apparently been altered in some way by the IA, presumably to its advantage. If the IA enters the endothelial cell and alters intracellular function to suit its own purposes, then the endothelial macrophage becomes a subverted pawn of the IA and a pathologic component, fostering the progression of the disease process.

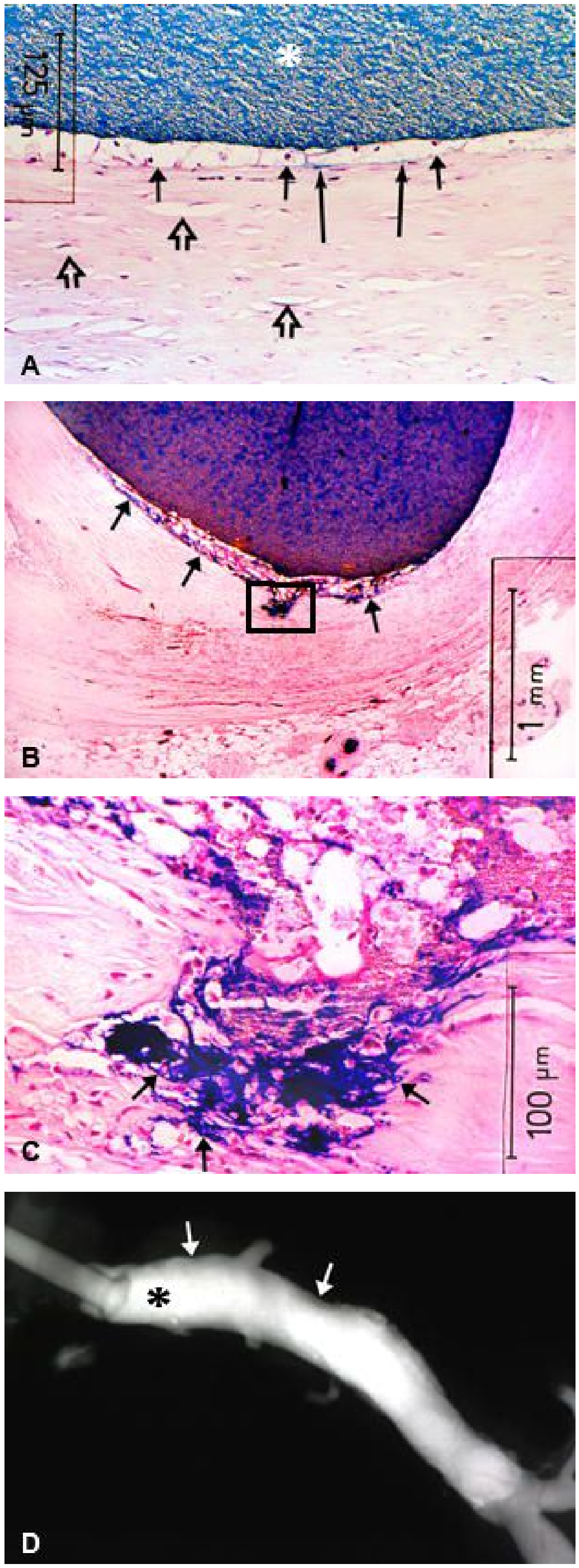

Figure 17B and C, show a surface erosion or a superficial ulceration involving the endothelial and subendothelial tissue that is much more extensive than that in Figure 17A and is associated with many loosely attached macrophage foam cells. This erosion involves a rather sizable portion of the luminal circumference. It is also associated with a rather deep penetrating ulcer near the center of the plaque. Close examination of the tissue interface at the base of the erosion shows evidence consistent with active digestion and destruction of plaque tissue (Figure 17C). This histologic picture is of an active, expanding, spreading, destructive process involving the endothelial and subendothelial surface in an erisipelas-like fashion. In addition, since the destructive changes are most severe in the central portion of the erosion, this area may have been the initial focus of injury. Note also that the depth of the superficial erosion tends to taper in both directions from the central area to the lateral extent of the erosion in Figure 17B. The IA seems to have estab lished a focus of injury in the central part of the erosion, then spread contiguously in a circumferential direction. The central, penetrating ulceration shows the IA is also spreading downward toward the center of the plaque toward the necrotic core. This picture of a spreading destructive IA, localized to the endothelial surface, is similar if not identical to the spreading destructive process, proposed in Chapter 1 and 4, involving the center of the plaque and the formation of a necrotic core.

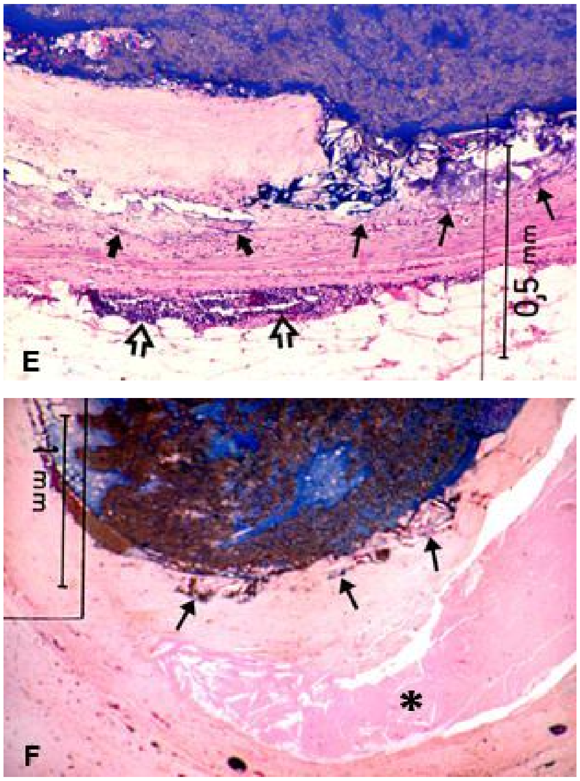

Figure 17: **A**, Endothelial cells have transformed into foam cells (short arrows) overlying an atherosclerotic plaque in the mid-RCA of a 76-year-old white female. Endothelial integrity has been breached, with injection mass visible beneath these foam cells (long arrows). Lipid-laden SMCs are present in the underlying plaque tissue (open arrows). White asterisk = lumen. H & E stain. **B** and **C**, Same patient as in **A**, but approximately 1 cm distal to **A**, shown in low-power (**B**) and high-power (**C**). A surface erosion has destroyed a portion of the endothelium (arrows), subendothelial tissue, and, in addition, a deep ulceration (rectangle) appears to be penetrating into the plaque in the direction of the necrotic core. Many foam cells and considerable tissue debris are present. In **C**, note the irregular, moth-eaten border of the ulceration (arrows), consistent with digestion and destruction. **D**, X-ray of dissected RCA of a 38-year-old white male who died SCD outside the hospital. There is no evidence of significant luminal obstruction, but the luminal margins are fuzzy and indistinct in the proximal 1/3 of the artery (arrows). Asterisk = RC ostia with cannula in place. **E**, A typical section taken from the proximal portion of the artery shown in **D**. Large portions of the intima have been destroyed down to the internal elastic lamina (thin arrows). A small focus of calcification is present (fat arrows) plus marked adventitial inflammatory response (open arrows). Considerable tissue debris and microemboli fragments are present in the lumen. H & E stain. **F**, Superficial erosion and partial destruction of the fibrous cap (arrows) overlying a large necrotic core (asterisk) of a 86-year-old white male who died SCD in the hospital. H & E stain.

Proteolytic Enzymes

The spread of the IA and the destruction of endothelium and subendothelial tissue may be promoted by production of proteolytic enzymes, such as MMPs, by the macrophage foam cell, possibly through stimulation by oxidized LDL [113]. These proteolytic enzymes can digest and break down surrounding tissue, and have been shown to play a key role in PU and rupture [37,114]. Perhaps they play a similar role in facilitating the spread of the IA at the endothelial surface. Perhaps the production of these proteolytic enzymes is also the result of altered intracellular mechanisms, produced by the IA to foster its spread along the endothelial surface.

Longitudinal Spread of the IA

Figures D and E, illustrate an extreme case of surface erosion involving the proximal 5cm of the right coronary artery of a young male who died sudden cardiac death (SCD) outside the hospital.

Eighteen contiguous coronary segments, beginning at the RC ostia, were involved with this erosive process which included virtually the entire luminal surface of each segment. It was almost as if a corrosive acid had been poured down the artery. The endothelium was eroded and the intima was virtually destroyed down to the internal elastic lamina in a number of places (Figure 17E), but no significant mural thrombi were present at any site. The postmortem angiogram, (Figure 17D), shows no significant luminal stenosis, but there are areas of calcification and considerable evidence of T cell infiltration in the adventitia, consistent with active, ongoing injury (Figure 17E). This particular case shows that the IA is able to spread, not only in a circumferential direction, but also longitudinally along the endothelial surface. The magnitude and extent of the surface erosion may reflect the inherent pathogenicity of the IA.

Destruction of the Fibrous Cap

Figure 17, figure F illustrates a surface erosion that involves the fibrous cap overlying a large necrotic core. The center of the fibrous cap is undergoing erosion and destruction from the luminal side, but this destructive process has not yet penetrated into the necrotic core - shown by the absence of injection mass in the core. Destruction of the central portion of the fibrous cap is potentially more serious than a shoulder ulceration because the center of the core will be exposed to flowing blood, increasing the potential for acute thrombosis and acute coronary events. Surface erosion, independently or in conjunction with erosion from beneath the fibrous capm [67], is another mechanism of PU that can lead to acute coronary events.

Absence of Resolution

A brief review of the illustrations in Figure 17 shows that none of these erosions is associated with evidence of resolution or healing. That is, there is no evidence of mural thrombosis, even though large amounts of subendothelial collagen are exposed, nor is there evidence of the hypercellular response that would be expected in the normal resolution of injured tissue. Certainly there is no neointimal, FP response resembling that seen following PTCA. The IA, directly or indirectly, apparently prevents such responses. Presumably, there are also inheremt thrombolytic factors acting at the site of erosion that prevent thrombosis and other normal healing responses. Therefore, a surface erosion over an atherosclerotic plaque is not an ordinary injury in which the IA comes and leaves quickly, followed by resolution, but is consistent with an IA that continues to be present and active on a long-term basis. Because the natural history of these surface erosions has not been determined, they may exist as chronic, festering lesions and persist for indefinite periods invading, expanding, and destroying the fibrous cap. Such chronic lesions could result in elevation of acute phase reactants, like fibrinogen and C Reactive Protein, that persist for long periods of time [115,116].

Frequency of Surface Erosions

A previous study from this laboratory showed that approximately 25% of all UPs that are present WITHOUT luminal thrombosis are of the surface erosion type, often multiple in any given patient [57]. They are consistently associated with infiltration of T cells into the adventitia, and to calcification of the artery wall, all indications of active, progressive atherosclerotic disease. The vast majority of these superficial erosions are not associated with significant luminal stenosis. They may be relatively asymptomatic. However, in the presence of significant luminal stenosis, these surface ulcerations may form the substrate for occlusive thrombosis and acute coronary events [110]. Surface erosions are not benign lesions, even though they may be currently asymptomatic, not associated with luminal stenosis.

Significance of These Findings

Surface erosions offer further information on the nature of the IA, showing it to be capable of attacking, localizing, and destroying the endothelial and subendothelial tissue overlying an atherosclerotic plaque. If these findings are correct, it should be possible to find the IA in the area immediately surrounding a surface erosion. This also means that any therapeutic agent designed to neutralize, kill, or remove the IA can readily reach the IA in this superficial location, as opposed to an IA buried deep within a plaque.

In Review

Surface erosions are probably caused by the same IA responsible for initiation of the plaque and formation of the necrotic core. The IA, directly or indirectly, appears to alter and subvert intracellular functions, converting endothelial macrophages into pathologic components of the disease process. The evolutionary purpose of these alterations may be to create intra and extracellular conditions favorable to the growth and replication of the IA. Replication and growth of the IA inevitably lead to and result in the spread of the IA in all directions from a central focus. This is aided by the production of MMPs by macrophage foam cells. Surface erosion and associated destruction of the fibrous cap by the IA may contribute to PU, thrombosis and acute coronary events. Surface erosions may exist as chronic lesions for long periods of time without resolution or healing, producing chronic elevations of C Reactive Protein, Fibrinogen, and other acute phase reactants. Surface erosions are very frequent in patients with ACD and are a component of active, progressive atherosclerosis. They may serve as a substrate for acute thrombosis when underlying luminal stenosis approaches 80% of the cross-sectional area [57].